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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,159	06/27/2001	Shigeru Kawahara	206269US0PCT	9776

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1621

DATE MAILED: 08/26/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,159	KAWAHARA ET AL.	
	Examiner	Art Unit	
	Paul A. Zucker	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 May 2003 has been entered.

Current Status

2. This action is responsive to Applicants' Request for Reconsideration of 27 May 2003 in Paper No 17.
3. Claims 5-15 remain pending.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 5-15 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 5-15 fail to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 17 filed 27 May 2003. In that paper, applicants have stated that the crystal having the X-Ray Powder Diffraction (XRPD) spectrum set forth in Figure 1 of the same submission corresponds to that for the crystal of the

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invention, and this statement indicates that the invention is different from what is defined in the claim(s) because the claims set forth only a small subset of the peaks therein. The entire XRPD spectrum is characteristic of a particular crystalline form. Claims 5 and 12 recite selected peak values as characteristic of the x-ray diffraction pattern of a particular crystalline form of N-[N-(3,3-dimethylbutyl)-L—aspartyl]-L-phenylalanine methyl ester. This is an insufficient means of characterization of the XRPD spectrum that renders claims 5 and 12 and their dependents different from the invention which is characterized by the entire spectrum. Applicants should amend these claims to refer to the figure of the XRPD spectrum of the claimed crystalline compound or set forth the position and intensity of all significant peaks that appear in the diffraction spectrum.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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5. Claims 5 –9 and 11 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Claude et al (US 5,510,508 04-1996).

Claude discloses (Column 4, lines 18-26) a process for the crystallization of N-[N-(3,3-dimethylbutyl)-L—aspartyl]-L-phenylalanine methyl ester (Neotame) from water-methanol solution which contains little or no methanol. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

In the alternative, the invention as a whole is obvious over the disclosure of Claude since it provides no patentable modification of the process as disclosed by Claude: recrystallization of Neotame from a water-methanol solution at a temperature below 40°C.

Instantly claimed is a method for the crystallization of N-[N-(3,3-dimethylbutyl)-L—aspartyl]-L-phenylalanine methyl ester (Neotame) to obtain crystals having a specified set of characteristic peaks. Claude further discloses (Column 4, line 19) that crystallization is carried out below 40°C.

Claude teaches (Column 4, lines 18-26) a process for the crystallization of N-[N-(3,3-dimethylbutyl)-L—aspartyl]-L-phenylalanine methyl ester (Neotame) from water-methanol solution which contains little or no methanol. Claude is silent with respect to the exact amount of methanol in solution but indicates that methanol is removed

by evaporation and thus a low concentration or absence of methanol (cf. instant limitation in claim 7 of "15 wt.% or less" methanol content) can be assumed. Claude further teaches (Column 4, line 19) that crystallization is carried out below 40°C. This is within 10°C of the temperature of 30°C claimed as a lower limit in the instant case (Claim 9). It is therefore reasonable to assume that crystallizations performed at 35 °C, for example, under the conditions described by Claude will have the same diffraction characteristics as those claimed in the instant application. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. Small adjustments in solvent ratios in the solvent composition disclosed by Claude to achieve the optimum result from the crystallization process would be well within the skill of one of ordinary skill in the art.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to purify Neotame, a compound used as an artificial sweetener for human consumption. The expectation for success would have been high since the starting material, solvent composition and product are the same as that taught by Claude.

Claim Rejections - 35 USC § 103

6. Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claude et al (US 5,510,508 04-1996) in view of Tosoh et al (WO 93/02101 02-1993).

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Instantly claimed is a method for the crystallization of N-[N-(3,3-dimethylbutyl)-L-aspartyl]-L-phenylalanine methyl ester (Neotame) to obtain crystals having a specified set of characteristic peaks. Further claimed is the use of seeding to generate the desired crystalline form.

Claude teaches (Column 4, lines 18-26) a process for the crystallization of Neotame from water-methanol solution which contains little or no methanol. It is therefore assumed that crystallizations under the conditions described by Claude will have the same diffraction characteristics as those claimed in the instant application.

The method of Claude differs from the instant method in that Claude is silent with regard to the use of seeding to generate the desired crystalline form. Such use of seeding, however, is standard practice in a crystallization experiment when seed crystals are available.

Tosoh, in fact, teaches (Page 4, lines 5-1) the use of seeding to preferentially form crystals of aspartame having the desired properties. Aspartame is an artificial sweetener very closely related in structure and properties to Neotame. Neotame can, in fact, be synthesized from aspartame in a single step. Tosoh's teaching demonstrates the well understood principle in organic chemistry that a preferred type of crystal can be obtained by seeding with that type of crystal. The invention outlined in claims 12-15 simply represents the application of standard laboratory practice to a

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previously disclosed process for producing crystals of Neotame, presumably having the required crystalline form.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to purify Neotame, a compound used as an artificial sweetener for human consumption. The expectation for success would have been high since the starting material, solvent composition and product are the same as that taught and seeding-a commonly used technique in crystallization experiments -was employed.

***Response to Applicant's Arguments with Regard to These Rejections
Response to Applicant's Declaration***

7. The declaration under 37 CFR 1.132 filed 27 May 2003 is insufficient to overcome the rejection of claims 5 –9 and 11 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Claude et al (US 5,510,508 04-1996) or the rejection of claim 12-15 under 35 U.S.C. 103(a) as being unpatentable over Claude et al (US 5,510,508 04-1996) in view of Tosoh et al (WO 93/02101 02-1993) as set forth in the last Office action because: Applicants have not provided a true side –by-side comparison as detailed below:

- a. Declarant's Experiment I (Declaration, page 7, line 21 – page 9, line 9), is generally faithful to the disclosure of Claude. However, it assumes that Claude's teaching that a temperature of below 40°C is maintained during evaporation/crystallization means that the *bath* temperature is maintained at the required temperature and not the crystallization solution itself. The Examiner contends that Claude teaches control of the temperature of the

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solution itself. No external bath is even implied by the disclosure of Claude.

For this reason Declarant's Experiment I does not represent a true side-by-side comparison.

- b. Declarant's Experiment II (Declaration, page 7, line 21 – page 9, line 9), in contrast to Experiment I (with the above-noted exception), is not a true side-by-side comparison with Example 2 of Claude et al for the following reasons:
 - i. Declarant's Experiment II is carried out on a markedly larger scale than that of Claude (600+% larger based on aspartame). Aside from the difficulties introduced by scale-up, the relative amounts of reagents employed are not proportional. Based on the use of 30.64 gm aspartame:
 - 1. 15.62 grams of 3,3-dimethylbutyraldehyde should be employed versus 15.00 gms in the instant case.
 - 2. 368 cm³ of 0.1 M aqueous acetic acid should be employed versus 353 gms in the instant case.
 - 3. 6.128 gms of 10% palladium on carbon should be employed versus 5.88 gms in the instant case.

While the difference in amount of reagent in each case is small, the cumulative effect of all the differences on the reaction may not be.

In addition,

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- ii. Declarant's Experiment II is carried out at 30⁰C while that of Claude is carried out at room temperature (generally considered to be 18⁰C-20⁰C).
- iii. The instant reaction is carried out for 19 hours while that of Claude is carried out for 2 hours.

For the above indicated reasons Applicants' declaration is unconvincing.

In addition the Examiner notes that the declaration provides further support for the requirement that the entire XRPD (X-Ray Powder Diffraction) spectrum be incorporated into the claims. Declarant's experiments (Declaration, page 9, lines 1-3 and page 11, lines 11-14) which produce an additional, unidentified, "crystal type" underscore the possibility that additional, as yet undiscovered, "crystal types" that share the same "characteristic" peaks may exist. Declarant has not, in fact, demonstrated that the new "crystal type" does not possess the instantly claimed characteristic peaks in addition to the indicated peaks. The use of characteristic peaks is thus deemed to insufficiently characterize the claimed crystal.

Conclusion

8. Claims 5-15 are pending. Claims 5-15 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

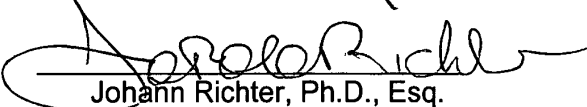
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker
Patent Examiner
Technology Center 1600

August 15, 2003


Johann Richter, Ph.D., Esq.
Supervisory Patent Examiner
Technology Center 1600